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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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08/487,623 06/07/95 LOVGREN

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EXAMINER

HM21/0317

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SPIEGEL, C	PAPER NUMBER
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1645

DATE MAILED: 03/17/98

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 12/8/97

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- ☒ Claim(s) 6, 7, 10, 13, 16-18 is/are pending in the application.  
Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
☐ Claim(s) \_\_\_\_\_ is/are allowed.  
☒ Claim(s) 6, 7, 10, 13, 16-18 is/are rejected.  
☐ Claim(s) \_\_\_\_\_ is/are objected to.  
☐ Claim(s) \_\_\_\_\_ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.  
☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.  
☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.  
☐ The specification is objected to by the Examiner.  
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).  
☒ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been  
☐ received.  
☒ received in Application No. (Series Code/Serial Number) 08/182550  
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☐ Notice of Reference Cited, PTO-892  
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s) \_\_\_\_\_  
☐ Interview Summary, PTO-413  
☐ Notice of Draftsperson's Patent Drawing Review, PTO-948  
☐ Notice of Informal Patent Application, PTO-152

-SEE OFFICE ACTION ON THE FOLLOWING PAGES-

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***WITHDRAWAL OF FINALITY***

In view of the APPEAL BRIEF filed on December 8, 1997 (paper no. 14), PROSECUTION IS HEREBY REOPENED. New and/or modified grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

- (a) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,
- (b) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

***CHANGE IN ART UNIT***

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1645.

***BACKGROUND DISCUSSION***

It is the understanding of the Examiner, based upon the specification, that the invention is drawn to microparticle based bioaffinity reactions which uses the least amount of affinity microparticles practical in order to maximize the concentration of analyte and/or labeled affinity

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reagent ultimately bound to microparticles by virtue of the bioaffinity reaction, thereby maximizing available signal per microparticle for measurement. In order to preserve signal which may otherwise be lost by washing steps or other additional liquid handling and/or dilution steps, it is the understanding of the Examiner, based upon the specification, that the signal from the reacted microparticles is individually measured (although more than one microparticle reading may be relied upon for improved reproducibility/reliability), and concentration is determined from a standard curve which correlates analyte concentration with signal strength from the same number of measured microparticles. In the specification see especially, the abstract, page 2, lines 7-17, page 10, lines 1-5, page 6, lines 9-27, page 8, lines 29-33, and page 9, lines 30-33.

However, the claimed invention does not clearly and particularly point out use of a **decreased** amount of microparticles *vis-a-vis* the prior art, although applicant repeatedly emphasizes this point when proffering an explanation as how the claimed invention differs from routine optimization of assay parameters in a particle-based assay and from the applied prior art. See e.g. Rule 115 amendment filed December 8, 1996 (paper no. 9) at ¶ bridging pages 10-11, page 12, ¶¶ 2 and 3; and, Brief filed December 8, 1997 (paper no. 14) at ¶ bridging pages 4-5.

Assuming *arguendo* that the amount of microparticles used is **not** decreased from that of the prior art, then

Appellants' invention is the discovery that the analyte concentration in a sample can be measured from the surface of a single microparticle by adjusting the relative amounts of microparticles and sample. (see Brief ¶ bridging pages 7-8)

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However, **the record is confusing**. See e.g. applicant's response filed December 10, 1996 in the paragraph bridging pages 4-5

Claim 13 has been amended to precisely recite that in the biospecific assay method of the present invention analyte concentration in a sample is determined by measuring the signal strength from an individual microparticle using a measuring means capable of reading the luminescence from an individual microparticle and comparing the signal strength from the individual microparticle with a standardization curve. **In the method of the invention each of the individual microparticles is not separately measured.** (emphasis added)

Therefore, it is respectfully submitted that an appeal to the Board of Patent Appeals and Interferences is premature because a core issue of patentability has **NOT** been crystallized, i.e. what exactly is applicant's invention -- (1) a decreased number of microparticles *vis-a-vis* the optimized number of the prior art? Possibly, but not necessarily, according to the Brief; (2) determination of analyte concentration based upon the strength of label signal bound to a single individually measured microparticle? Yes, but No.

#### ***PRIOR CITATION OF TITLE 35 SECTIONS***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

#### ***DRAWINGS***

The drawings are objected to for reasons of record (see PTO-948 attached to paper no. 7). Correction is required.

#### ***THE INVENTION and THE PROBLEM***

According to the Brief,

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[t]he invention is the discovery that by appropriate control of the amount of microparticles and the amount of sample, the concentration of an analyte in a predetermined, clinically relevant range of analyte can be determined by measurement of signal from a surface of a single microparticle. (sentence bridging pages 2-3)

This begs the question as to whether or not analyte concentration **IS** determined by measurement of signal from a surface of a single microparticle.

***REJECTIONS UNDER 35 U.S.C. § 112***

***Second Paragraph***

Claims 6, 7, 10, 13 and 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 is unclear as to what criteria are used to “predetermine” the amount of microparticles and sample so as to correlate measurement of a single microparticle to analyte concentration, i.e. how does the “predetermined” amount of microparticles and sample volume of the improvement step differ from the microparticle and sample volumes of the preamble in this Jepson claim. Measurement analyte concentration from the signal measured from a single microparticle implies a critical relationship between the amount of sample analyte concentration expected in a predetermined volume of sample and the amount of affinity microparticles used. Critical limitations should be positively stated not merely implied.

***First Paragraph***

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Claims 6, 7, 10, 13 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It is unclear how the claimed invention differs from routine optimization in determining a “predetermined” amount of affinity microparticles and sample volume which would not spread the bottom end of analyte concentration over so large a surface area as to render bound analyte-specific label indistinct from non-specific background label binding. The issue is NOT whether one of ordinary skill in the art would be able to measure an individual microparticle as of January 18, 1994. It is admitted that individual microparticles or “cells” can be measured by techniques such as flow cytometry, CCD microscopy, etc. The issue is how the instant “predetermination” of affinity microparticles and sample differs from routine optimization.

In paper no. 9 applicant argued this is NOT optimization because the skilled artisan would NOT optimize by DECREASING the amount of microparticles being used. Rather the skilled artisan would INCREASE the binding surface when small amounts of analytes were to be measured. There is no evidence of record to indicate that this is the state of the art *per se*. It is respectfully submitted that multiple considerations are being balanced to optimize an assay. It is further submitted that it is generally accepted in the art that increasing the available binding surface area will increase the probability of analyte reacting with its binder and therefore decrease the overall assay time. However, such an increased surface area also increases the area over

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which differential signal is spread. A factor that the skilled artisan would have also been aware of and would have considered in optimizing the assay parameters.

***REJECTIONS UNDER 35 U.S.C. § 103(a)***

Claims 6, 10, 13 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soini et al. (US 5,028,545) in view of Ekins et al. (*Clinical Chemistry*, 37(11):1955-1967 (1991)).

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claim 13 above, and further in view of Bush et al. (*Analytical Biochemistry*, 202:146-151 (1992)).

Soini et al. describes high detection sensitivity biospecific assay methods using time-resolved fluorescent tracers and microparticles coated with analyte specific bioaffinity reactants using flow cytometry and microfluorometric measurement systems (col. 1, lines 27-56; col. 2, lines 20-37). Soini et al. differs in failing to disclose explicitly, basic concepts used to optimize biospecific assay methods, e.g. the interrelationship between sample analyte and assay reactants used to provide maximal sensitivity as instantly claimed such that concentration of an analyte in a predetermined, clinically relevant range of analyte can be determined by measurement of signal from a surface of a single microparticle.

Ekins et al. teaches all immunoassays rely on the measurement of antibody (i.e. bioaffinity reactant A) occupancy by analyte. Ekins et al. further teaches that if the amount of antibody is vanishingly small, fractional antibody occupancy is independent of both the amount of antibody

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concentration and sample volume. While Ekins et al. exemplifies adjustment of antibody concentration and sample, i.e. analyte, concentration to optimize a microspot immunoassay, Ekins et al. explicitly comments on the generic applicability of the teachings therein (see the entire article).

Bush et al. is added to show the applicability of time-resolved fluorescent labelled microparticle based assays to hybridization formats.

Therefore, minus a showing of unexpected results, it would have been obvious to combine the generic optimization procedure of the Ekins et al. school in any given biospecific assay method, such as the fluorescent labelled microparticle based assay of Soini et al. or Bush et al., in order to obtain maximum sensitivity and/or minimize random errors as suggested by Ekins et al. In addition, one of ordinary skill in the art would have considered at least the following factors in optimizing a given biospecific assay: the expense of bioaffinity reagents, the clinically (or otherwise) significant result range, the type of sample being assayed, the specificity and affinity of the bioaffinity reagent for analyte, the desired time to result, etc.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure,

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such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant newly argues Soini has been wrongly interpreted. Soini has nothing to do with fractional occupancy and, therefore, is not combinable with Ekins et al.

It is agreed that the rejection incorporating Bush rises or falls with Soini-Ekins.

In response, Soini explicitly recites “measuring the concentration of analyte on each microsphere” on the basis of bound label (col. 1, lines 53-55). Soini explicitly teaches incubating sample, microspheres and labelled reactants “in smallest possible volume” to achieve a complete reaction in a short time (col. 2, lines 20-25). Soini discusses analyzing a “sufficient number” of microspheres but does NOT discuss what “number” of microspheres are initially chosen for reaction., i.e. how to predetermine the amount of microspheres and sample used in the “smallest possible volume”. The precise point(s) of “misinterpretation” is NOT understood. Soini is SILENT as to whether fractional occupancy or another particular optimization criteria are used.

Secondly, as to Ekins et al., it is respectfully submitted that the instant “microparticle” is analogous to the “microspot” of Ekins et al. and the “predetermined number of microparticles” is analogous to the “microdisc” of Ekins et al. which can be defined as the total number of microspots.

The rejections of claims 6, 7, 10, 13 and 16-18 under 35 U.S.C. § 103(a) over concentration of an analyte in a predetermined, clinically relevant range of analyte can be determined by measurement of signal from a surface of a single microparticle Soini et al. (US

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5,028,545) in view of Buechler et al. (US 5,089,391) alone or further in view of Bush et al. (*Analytical Biochemistry*, 202:146-151 (1992)) are withdrawn in view of applicant's arguments.

**REMARKS**

The arguments filed by Brief on December 8, 1997 have been fully considered but are not deemed convincing of patentability for the above reasons. Applicant's representative is invited to telephone the undersigned if he/she feels it would advance the disposition of this case. In summary, it is respectfully submitted that applicant's invention has not yet been clearly claimed with particularity and specificity so as to distinguish it over the prior art; and, that the Soini-Ekins prior art rejection is based upon optimizing the reactants of Soini using the fractional occupancy theory of Ekins wherein the instant "microparticle" is analogous to a "microspot" of Ekins (and the total number or "predetermined" amount of microparticles is analogous to the "microdisc" of Ekins).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carol A. Spiegel whose telephone number is (703) 308-3986.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Paula K. Hutzell, can be reached on (703) 308-4310. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Carol A. Spiegel  
March 15, 1998

*Carol A. Spiegel*  
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